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Diagnostic and therapeutic strategies in hyperoxaluria: a plea for early intervention

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there is a certain overlap with severe forms of secondary hyperoxaluria [9,10].

Introduction

Oxalic acid is an end product of human metabolism and does not appear to be needed for any process in the body. Under normal conditions the daily load of oxalate deriving from endogenous production and intestinal absorption is fully excreted by the kidneys. Up to a certain extent renal oxalate excretion may even keep pace with an elevated oxalate load, yet at the expense of hyperoxaluria, a major risk factor for recurrent nephrolithiasis and nephrocalcinosis [1,2]. Unfortunately, hyperoxaluria is all too often overlooked at this stage. The situation becomes far more serious if renal function is impaired (e.g. from complications of hyperoxaluria): the amount of oxalate excreted in the urine will no longer match its production and absorption, resulting in progressive oxalate retention with renal and extrarenal deposition of calcium oxalate, i.e. systemic oxalosis [3]. In a recent survey from the US ~30% of patients with primary hyperoxaluria (PH) were only diagnosed after having reached end-stage renal failure (ESRF [4]). Late diagnosis is a particular problem in adult patients. In a recent Dutch study, 59% of those patients older than 18 years had already reached ESRF at the time of diagnosis of PH I [5].

Two forms of autosomal-recessive inherited PHs have been characterized at the molecular level, both being due to defects of glyoxylate metabolism [6–8]. One or several other types of PH are likely to exist, and

Diagnosis

The hallmark of type I and II PH is a strongly elevated urinary excretion of oxalate ($>1\text{ mmol}/1.73\text{ m}^2\text{ BSA/day}$, normal <0.5) [1]. Urinary oxalate excretion in secondary hyperoxaluria is usually $<1.0\text{ mmol}/1.73\text{ m}^2\text{ BSA/day}$ [2] (Figure 1). Urinary oxalate over creatinine ratios may be used for screening in children as long as age-specific normal values (for age <2 years, <300 ; for age 2–5 years, <130 ; for age 5–15 years, <70 and for age >16 years, $<40\text{ mmol/mol}$) are at hand [11]. However, the ratios need to be confirmed by complete urine collection. Urinary glycolate excretion is elevated in most patients with PH I, whereas urinary L-glyceric acid excretion is increased in nearly all patients with PH II. Hence, isolated hyperoxaluria does not exclude with certainty either type of PH. On the other hand, hyperoxaluria plus elevated excretion of either glycolate or L-glyceric acid is a strong argument but no proof for this diagnosis (PH I or PH II) [9,10].

Caution is needed in the interpretation of urinary values in recurrent stone formers who are not stone free at the time of urine collection, as calcium and oxalate are deposited continuously, leading to ongoing stone growth and hence to a lower urinary excretion [12]. On the other hand, a high oxalate diet (e.g. spinach, rhubarb juice, etc.) on the day of urine collection must be avoided, as it would definitively increase the urinary oxalate levels.

The finding of pure CaOx mono-hydrate (whewellite) stones is a hint to the diagnosis of PH. Stones of patients with secondary hyperoxaluria are usually mixed (whewellite and weddellite) [10,13].

Values of urinary oxalate are falsely low in patients with renal insufficiency because of oxalate retention and systemic deposition as calcium oxalate, hence

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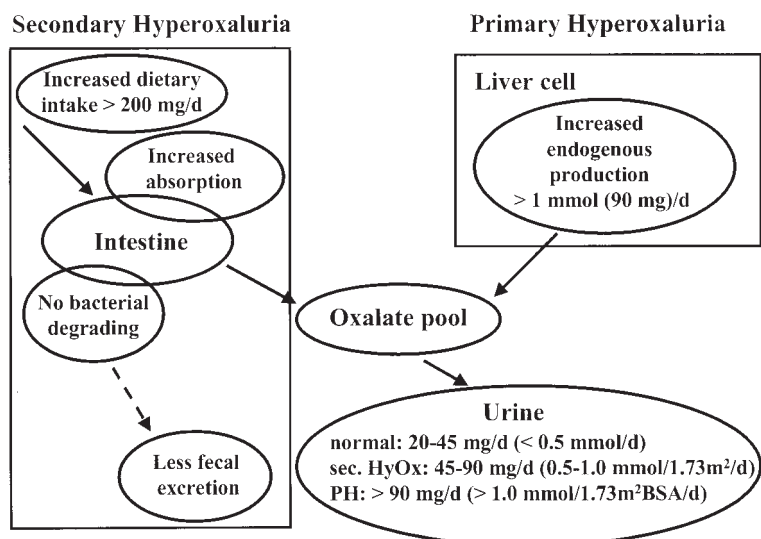


Fig. 1. Pathways of primary and secondary hyperoxaluria.

hyperoxaluria may be missed. Determination of plasma oxalate (P_{Ox}) can help in this situation. Normal levels of P_{Ox} range from 0.5 to 7.5 $\mu\text{mol/l}$ depending on the method used [1,14], with 10 $\mu\text{mol/l}$ being the upper cut-off point in our lab. The increase of P_{Ox} is inversely correlated with the fall of GFR, being significantly higher in PH patients, compared with non-PH patients in renal insufficiency [15].

Data of urinary oxalate in ESRF cannot be used in contrast to plasma levels of oxalate and glycolate [16]. Patients with PH have significantly higher P_{Ox} levels ($>80 \mu\text{mol/l}$) than non-PH patients in ESRF ($<60 \mu\text{mol/l}$) [17]. Plasma glycolate levels are significantly elevated in PH I patients only once they are on renal replacement therapy [16]. The finding of birefringent CaOx crystals at a bone or kidney biopsy is strongly suggestive of PH, and an eye ground examination showing crystal retinopathy is virtually diagnostic [1].

Liver biopsy for enzymatic analysis is needed for definitive diagnosis if liver transplantation is considered, unless the genotype is known or diagnosis has been confirmed in a sibling. DNA analysis as a diagnostic procedure is not a standard technique except in populations with a high frequency of a specific mutation [1,18].

If these diagnostic procedures do not yield a definitive diagnosis, further evaluation is recommended before specific therapy is started. Another recently reported cause of significant secondary hyperoxaluria is the absence of oxalate degrading bacteria such as *Oxalobacter formigenes* and, allegedly, other species (*Enterococcus faecalis*, *Eubacterium lentum* and lactic acid bacteria) in the gut [19–21]. The obligate anaerobe bacterium *O. formigenes* degrades oxalate to formate, which is further metabolized and excreted via the faeces [2,19]. It is found in the intestinal tract in the majority of the adult population (70–80%) and protects them from increased intestinal oxalate absorption and

ensuing hyperoxaluria. Identification of *Oxalobacter* in stool samples is possible with the PCR technique. Recurrent calcium oxalate stone formers and patients with malabsorption syndromes or patients with hyperoxaluria of unknown origin often lack *Oxalobacter*. This might be due to antibiotic treatment (e.g. in patients with cystic fibrosis), or to specific therapy of the underlying disease (e.g. in Crohn's disease) [2,22]. Increased intestinal oxalate absorption can be assessed by an absorption test using [$^{13}\text{C}_2$]oxalate [23]. It helps to identify hyperabsorbers, who need specific therapy (e.g. low oxalate, high calcium diet), and to differentiate between primary and secondary forms of hyperoxaluria. It is easy to perform and without risks, as the isotope used is stable.

Conservative treatment

Measures to lower the oxalate load

Primary hyperoxaluria. Pyridoxal phosphate is an essential cofactor of AGT and pharmacological doses of pyridoxine may significantly reduce hyperoxaluria. About one-third of PH I patients are pyridoxine sensitive [1]. Pyridoxine is started with 5 mg/kg body weight/day and is stepwise increased up to 20 mg/kg day, in order to exclude or demonstrate pyridoxine responsiveness ($>30\%$ reduction). A trial over some months is warranted in all PH I patients.

Secondary hyperoxaluria. A dietary advice is necessary (high calcium, low oxalate diet). The use of oxalate degrading bacteria like *Oxalobacter* to reduce the amount of oxalate available for intestinal absorption could become an option (perhaps even in the primary form of hyperoxaluria as an additional measure) [24,25]. Sidhu *et al.* [26] reported successful and safe recolonization of *O. formigenes* in rats, leading to a reduction of urinary oxalate excretion. Campieri

et al. [21] treated five hyperoxaluric patients with a preparation of lactic acid bacteria (Oxadrop) and observed a significant and persistent reduction in urinary oxalate excretion over time.

Measures to increase the urinary solubility of calcium oxalate

Most important is a high fluid intake (3–4 l/day) accompanied by the administration of either alkali (K^+/Na^+)-citrate [0.3–0.5 meq (0.1–0.15 g)/kg body weight/day] or orthophosphate (20–60 mg/kg body weight/day) [1].

Dialysis

No form of dialysis, not even the combination of routine haemo- and peritoneal dialysis is able to keep up with the endogenously produced oxalate, let alone to reduce the body oxalate burden [27,28]. In fact, the weekly oxalate elimination via haemo- or peritoneal dialysis ($\sim 6\text{--}9\text{ mmol/week}/1.73\text{ m}^2\text{ BSA}$) only equals the endogenous oxalate production of 2–3 days [27]. Hence, intensified haemodialysis with five to six sessions of 5 h/week and additionally nightly peritoneal dialysis may be considered until transplantation is performed. The higher the systemic oxalate burden the more oxalate needs to be excreted after transplantation, which further increases the risk of recurrence in the transplant. Apart from young age (< 5 years), a long period on dialysis (> 2 years) inevitably leading to massive systemic oxalate deposition is a specific risk for transplantation [9,29]. Hence, the dialysis period has to be kept as short as possible.

Transplantation in primary hyperoxaluria

Isolated kidney transplantation is an option only for the minority of patients responding well to pyridoxine [1,30], and, perhaps, for patients with late onset of ESRF (e.g. age > 50 years). As a result of the high risk of recurrence, combined liver/kidney transplantation is the treatment modality of choice in Europe. Isolated kidney transplantation is, however, still favoured in the USA, preferably from living related donors [30]. The medium term results are acceptable with actuarial survival of 84% for patients and 51% for grafts after 6 years; however, graft survival at 10 years is only 35% [30].

As the metabolic defect in PH I is confined to the liver, *combined liver/kidney transplantation* will cure the enzyme defect. Total hepatectomy of the patient's own and otherwise normal liver is necessary. Auxiliary liver transplantation is no option, as the oxalate overproduction by the patient's own liver would keep the process ongoing [1]. More than 100 combined liver/kidney transplantations have been performed in Europe since 1984 with an actuarial survival at 5 years (98 grafts in 93 patients) being 80% for patients and

71% for liver grafts. Renal function has remained stable with creatinine clearance of $40\text{--}60\text{ ml/min} \times 1.73\text{ m}^2\text{ BSA}$ after 5 years [1,29].

Additional haemodialysis or haemofiltration after transplantation is only required if (renal) graft function is inadequate. A steady high fluid intake (3–4 l/day) and medication to increase the urinary solubility of oxalate are needed during the first months because of the slow mobilization of the accumulated body oxalate [1]. Not only urinary oxalate excretion but also plasma oxalate and plasma calcium oxalate saturation remain elevated for several months or even years after successful combined liver/kidney transplantation [1,15].

Pre-emptive (isolated) liver transplantation is an option with the aim of avoiding ESRF [31]. However, as liver transplantation is not harmless and the optimal timing of transplantation is difficult to determine due to the unpredictable course of the disease, it is still not a generally accepted method for patients with PH I. Nevertheless, several patients with PH I not in renal failure have been treated this way with reasonable results [31]. Liver transplantation needs to be performed as long as kidney function is still appropriate ($\text{GFR} > 40\text{ ml/min}$, or even $50\text{--}70\text{ ml/min}$) [1,18].

Outlook

The time lag between the first symptom and the diagnosis often is far too long. Hence, the level of suspicion needs to be lowered and the diagnostic approach must be improved. Urinary oxalate excretion has to be assessed in every patient with calcium oxalate urolithiasis or nephrocalcinosis, and kidney stones require appropriate analysis. Waiting for the next lithotripsy session is by no means a preventive measure! Various therapeutic approaches are available, the ultimate goal being to prevent renal failure. Although PH type I would be a good candidate for gene therapy it is not yet applicable. Perhaps enzyme therapy through *O. formigenes* will become a therapeutic option.

Note: early diagnosis and treatment are mandatory in patients with PH to prevent a disastrous clinical course.

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